An Inside Look at FDA On-Site

There are over 18,000 establishments in the United States that manufacture, test, pack, and label drug products for humans. The Federal Food, Drug, and Cosmetic Act requires FDA to inspect each of these facilities at least once every two years. In addition, approximately 1,100 foreign facilities are periodically inspected.

Agency investigators, working from field offices in some 172 locations throughout the country, completed 3,661 domestic inspections in 3,230 human drug establishments in the fiscal year that ended Sept. 30, 1998. Another 356 inspections were done at 323 foreign establishments.

During that year, the agency took a number of legal actions to correct deficiencies for failure to meet drug manufacturing and product standards. These included three prosecutions, three injunctions, 19 seizures, and 244 warning letters. FDA also monitored recalls involving 264 drug products in various dosage forms.

An inspection can last from one or two days to several weeks, depending on its purpose and scope. There are three primary types of inspections: preapproval, postapproval, and surveillance good manufacturing practice (GMP) inspections.

Preapproval inspections are often initiated by the Center for Drug Evaluation and Research at FDA headquarters. While the center is reviewing a new drug application or abbreviated new drug application, it requests that the field office inspect the drug manufacturing facilities.

This inspection represents a significant step in the drug review process. The investigators must determine if the data submitted in the firm's application are authentic and accurate and if the plant is in compliance with current good manufacturing practice regulations. The district office recommends approval or disapproval of the application, based on its findings.

After the center approves an application and the firm is ready to start marketing the drug, FDA conducts a postapproval inspection, to evaluate the firm's validation studies. "Validation" refers to FDA's requirement that the firm show it can consistently manufacture a drug product within tight parameters from batch to batch, day to day, year to year. The investigators also verify that the firm has not changed its manufacturing, labeling, or quality control testing for that drug without filing a supplement to its application, and that the firm has not exceeded a tenfold "scale-up" in production.

"Scaling up" is the process of increasing the batch size for commercial manufacture. "For commercial production, FDA allows firms to manufacture their product in batches ten times larger than those produced for clinical or bioequivalency testing," Matthew Spataro, an investigator with the agency's New Jersey district office, says. "For example, if tablets were produced in batches of 100,000 during clinical testing, the commercial production batch cannot exceed 1 million tablets."

The investigators collect samples at both preapproval and postapproval inspections for analyses that will compare the composition of the product against known standards. The drug's chemical "fingerprint" must match the standard pattern for the compound. Samples are also collected to verify that the firm's laboratory methods are proper and consistent with the drug application.

Finally, a GMP, or "routine," inspection evaluates the firm's entire operations. Although pre- and postapproval inspections include examination of the firm's manufacturing practices, they are product-specific. GMP inspections, on the other hand, involve a comprehensive review of the firm's manufacturing operations.

When FDA's Matthew Spataro (right) arrives to inspect Knoll Pharmaceutical Company's manufacturing plant in Whippany, New Jersey, he shows his credentials and issues a written "Notice of Inspection" to Michael Corey, Knoll's Quality Assurance Manager. A full inspection may take weeks, while a visit to look at one or two specific things may take only an afternoon. An inspection team may comprise several people, including analysts, chemists, microbiologists, and investigators.

Before coming to the plant, Spataro, an FDA investigator with the New Jersey district office, reviews the plant's inspection history.

In the plant's receiving area, the investigator makes sure the firm is following its written procedures for receiving and handling incoming raw materials. He also evaluates the procedures to make sure they are adequate.

Early in the inspection, Spataro looks over the company's product complaint files. These files not only reveal how a firm conducts its complaint investigations, but they may also help investigators determine what areas to focus on in their inspection.

"If there are substantial problems or complaints about a product, we look at what kind of effort a firm puts into resolving the complaints," Spataro says. "If a firm is responsible for the problem, what is the corrective action taken? Did they look at manufacturing batch records? Did they review the laboratory analyses?"

"If there are excessive complaints about a particular product," Spataro adds, "the investigator may collect a sample from the reserve samples and have it analyzed at FDA's laboratory. A product that doesn't meet its predetermined specifications may be removed from the marketplace."

In the compressing area, precise amounts of materials are compressed for formulated products. Here, Spataro observes the operations that are essential for ensuring the quality of the product.

Spataro and Bob Stewart (left), Knoll's Manager of Packaging, review the label inspection system. Product labels are scanned for accuracy of batch number and expiration dates.

"A batch record is one of the most important documents in drug production because it tells the whole history of that batch," says Spataro. "It's a copy of the master record, the approved way to manufacture a particular product in a particular batch size. The record follows the batch production from one processing area to the next and records every step from beginning to end. Employee signatures document that the steps in manufacture, processing, packing, or holding were completed."

The record contains everything that happened concerning production of that batch—what went into it, where samples were taken, any problems encountered during manufacturing (such as equipment or power failure or a broken hose)—down to the exact batch yield.

If there is a problem with a product after it's on the market, Spataro says, one of the first things investigators do is examine the batch record for any problems—even those seemingly unimportant at the time—that may have occurred during manufacture.

Spataro checks to see if the equipment log accurately reflects the usage and cleaning of that particular vessel. Proper cleaning between uses is important to avoid contamination of products.

In the laboratory, Quality Control Senior Chemist Mila Cruza shows Spataro the results of a high-performance liquid chromatography (HPLC) assay she's performing on a finished product sample. The test is conducted to ensure the product conforms to standards and contains no impurities.

HPLC tests for the active ingredients of a formulation. "Every formulation has its own 'chemical fingerprint' that appears on the chromatogram as a distinct pattern of peaks," Spataro says: "If the pattern does not match the known standard, then a problem is apparent. Further tests can determine what the abnormal peaks represent.

"When we go into the laboratory, we make sure the HPLC and other instruments are working properly, check the quality of chromatograms, review what analytical methods are used and if they are appropriate and calculated correctly."

Spataro inspects some boxes from the warehouse where a firm may store products not yet distributed. Failed products that have not yet been destroyed would be stored in a separate reject area.

"An investigator may want to look at the reject area early on in the inspection for clues about what to key in on," says Spataro. "For example, if batches of a particular product have failed or been rejected, then that product will warrant a closer look."

Spataro observes Senior Quality Control Chemist Dale Kiddoo (right) setting up for a finished product USP (United States Pharmacopoeia) dissolution test. The dissolution test results determine how the tablets dissolve and whether or not they are suitable for marketing.